Value assessment and quantitative benefit-risk modelling of biosimilar infliximab for Crohn's disease

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Abstract:

Aim: Regulatory approval of biosimilars often depends on extrapolating evidence from one clinical indication to all of those of the originator biologic. We aimed to develop a quantitative benefit-risk analysis to assess whether the resulting increase in the uncertainty in the clinical performance of biosimilars (i.e. risk) may be countered by their lower pricing (benefit).

Methods: A one-year decision-analytic model was developed for the biosimilar infliximab (Inflectra®) for Crohn's disease. The perspective was that of the NHS in the UK and costs were valued to 2015/16. A hypothetical cohort of biologic-naïve patients with moderate-to-severe Crohn's disease were simulated through the model. Immunogenicity to infliximab was a key modifier, influencing rates of non-response and infusion reactions. Net health benefit was estimated based on quality-adjusted life years (QALYs). A range of sensitivity analyses tested the robustness of the results and explored how the biosimilar price must respond to varying immunogenicity to remain the preferred option.

Results: The base-case analysis predicted a positive incremental net health benefit of 0.04 (95% Central Range 0.00-0.09) favouring the biosimilar, based on 0.803 QALYs, and costs of £18,087 and £19,176 for biosimilar and originator, respectively. Two-way sensitivity analyses suggested that if 50% of patients developed antibodies, the value-based price of £410 per vial must be lower than that of the originator (£420), but remain higher than the actual market price (£378).

Conclusions: The model supports the use of Inflecta® for Crohn's disease in the UK, and provides a framework for the quantitative evaluation of biosimilars in the context of health technology assessment. Value-based pricing using this methodology could protect health systems from the potential risks of biosimilars where they are untested in the approved populations.

Key points for decision makers

- The base-case analysis predicts a positive incremental net health benefit of 0.04 (95% Central Range 0.00-0.09) favouring the biosimilar and suggests that if 50% of patients developed antibodies, the value-based price would need to be below the originator but higher than the current market price.
- The study presents a novel framework for the quantitative benefit-risk assessment of biosimilars, illustrated with biosimilar infliximab for Crohn's disease
- The methods provide an explicit framework for balancing risks (the uncertainty in the efficacy and harms of biosimilars) against their benefits (cost advantages)

1. Introduction

As patents for biological therapies expire, biosimilars, which are near identical versions of the originator products, are changing the therapeutic landscape [1]. Biosimilars are generally less expensive, or prompt a reduction in the price of the originator products while achieving comparable health outcomes. Medicines regulators seek assurance that there are no clinically meaningful differences in efficacy and safety to the originator [2,3]. This normally requires clinical trial evidence from a population sensitive to potential differences in efficacy, safety, or immunogenicity between the biosimilar and originator. Evidence of similarity in one clinical indication is assumed to extrapolate to other indications for which the originator product is approved based on the totality of the evidence, including the structural, physicochemical, functional, and non-clinical data in addition to clinical studies [2,3].

Biosimilars are not intended to be superior to the originator (these would be biobetters [4]) but there is a risk of an inferior safety profile (if only marginally). Uncertainties regarding the safety of biosimilars at the point of marketing authorisation are inherently related to the use of non-inferiority trials to justify near-equivalence of efficacy, the absence of trial evidence for all indications due to the process of extrapolation, and the lack of long-term experience and data [5,6]. The primary reason for adopting biosimilars and acceptance of the potential risks with no improved health benefits is the opportunity for cost savings. The biosimilar market in the US alone is forecast to save $54 billion in direct spending on biologic drugs from 2017 to 2026 [7].

The first biosimilar anti-TNFα approved in the EU, following the patent expiry of originator infliximab (Remicade®), was Inflectra®. Marketing authorisation was based primarily on evidence relating to non-inferiority in rheumatoid arthritis [8]; but regulatory experience with specific reference to Crohn's disease (CD) has been mixed, with some countries initially rejecting the drug or limiting its approved indications [9–11]. A key concern was that CD patients are more likely than others to develop antibodies to infliximab (ATI), which trials in other indications were unable to rule out [12,13]. The

consequences of developing ATI (immunogenicity) include reduced efficacy and increased likelihood of adverse events, particularly infusion reactions, which are rare but can be severe. Even minor differences between the biosimilar and originator have the potential to cause significant harm for patients [14].

With each new biosimilar, heath care payers therefore face the question of whether the cost savings can justify the increased uncertainty in their clinical performance. Health economic modelling can be used as part of the health technology assessment to evaluate the benefit-risk balance by pooling the available evidence and reflecting uncertainty in inputs, to estimate the likelihood of a biosimilar providing a net health gain [15]. The incremental net health benefit (INHB) between the biosimilar and originator represents the added value of the biosimilar considering both the reduced costs and the increased uncertainty surrounding its clinical performance given societal resource constraints [16] and, in effect, represents a quantitative approach to the benefit-risk assessment of biosimilars.

This analysis aimed to quantitatively assess the benefit-risk balance of biosimilar infliximab versus originator, to determine whether the cost savings justify the increased uncertainties in efficacy and safety, and to assess the value of conducting further trials in CD to reduce uncertainty in key parameters. The results are discussed in the context of emerging evidence from clinical use and ongoing trials in CD.

2. Methods

2.1. Model structure

We constructed a decision analytic model (decision tree) to compare the benefits and risks of infliximab (IFX) biosimilar and originator. We adapted a model of one-year cost-effectiveness of infliximab dose escalation versus initiation of adalimumab [17], identified from a MEDLINE review, by the addition of adverse events. A hypothetical cohort of 100,000 biologic-naïve 35-year-old 70-kg patients with moderate-to-severe CD was simulated through the model (Figure 1), which was structured over 4-weekly intervals. The perspective of the analysis was that of the National Health

Service (NHS) in the UK. For the purposes of the economic analysis, costs were restricted to those of the National Health Service (NHS) in the UK. Although CD is a chronic condition, a one-year time-horizon was justified, as the analysis focused on short-term outcomes.

Due to the concern regarding immunogenicity, the development of antibodies to infliximab (ATI) is an important modifier in the model, influencing the rate of primary and secondary non-response [18], and the likelihood of infusion reaction. Acute or severe infusion reactions take place within 24 hours of infusion, and delayed infusion reactions take place between 24 hours and 14 days after infusion [19]. In line with common practice [20], the disease states were defined by the Crohn's Disease Activity Index (CDAI): moderate-to-severe disease equates to a CDAI score ≥220, remission to a score <150 and response to a reduction in CDAI score ≥70 points, resulting in mild disease (≥150 CDAI score <220).

All patients entered the model in period 1 in moderate-to-severe disease state and received IFX therapy of 5mg/kg at weeks 0, 2 and 6, with infusions every eight weeks for those who respond, in accordance with the summary of product characteristics [21]. Initial response and the development of ATI were measured at week 12 (period 4). Those with no initial response ceased treatment with IFX, moved to standard care therapy in period 4, initially remaining in moderate-to-severe disease state. Standard care included all other possible therapies and surgeries [22].

Patients with primary response were in a mild disease state during periods 2 and 3 and entered ATI status-dependent remission or mild disease states in period 4. IFX maintenance therapy continued every 8 weeks unless they experienced secondary non-response (loss of response), or a severe infusion reaction, upon which they moved to standard care. Patients who experienced secondary non-response did so from a mild disease state. Acute and delayed infusion reactions were managed in the same period and IFX was not withdrawn. Patients could only experience one infusion reaction over the year and all were assumed to be in period 4, following the 4^{th} infusion, consistent with the findings of the pivotal clinical trial of maintenance infliximab (ACCENT I) [23].

At the end of one year, patients who remained on IFX could be in remission or experiencing mild disease or had moved to standard care or died. Patients receiving standard care could end the year in a moderate-to-severe disease state or post-surgical remission. Death in the model could result from age-specific, all-cause mortality, severe infusion reaction (SIR), surgery or disease flare. Age-specific, all-cause mortality [24] was applied during week 12, meaning none had experienced maintenance therapy.

Moves to alternative treatment or surgery occurred at the end of each period to allow for benefits, harms and costs to be allocated in whole periods. The impact of treatment benefits and harms were represented as utilities, from which quality-adjusted life years (QALYs) could be estimated. The effects of IFX treatment (and other biologics in scenarios) occur within the period of treatment. Standard care is assumed to take two periods to have effect [17]. Secondary non-response is assumed to take place at 38 weeks in line with the median in patients receiving the standard therapy of 5mg/kg of infliximab from ACCENT I [23]. The effect of IFX was assumed to wash out 19 weeks after stopping IFX due to a severe infusion reaction, in line with the median time to offset of response during placebo maintenance in ACCENT I [23].

The model was constructed in Microsoft Excel using visual basic language for probabilistic sensitivity analysis.

2.2. Model parameters

We obtained parameter estimates for ATI development, efficacy, adverse events, health utilities and costs from targeted MEDLINE literature reviews of clinical trials and previous cost-effectiveness models. All searches included the terms “Crohn’s disease” and “infliximab”, as well as other relevant terms depending upon the parameter, for example “loss of response”, “antibodies” and “drug sensitivity/or infusion reaction”. Model inputs are shown in Table 1.

2.2.1.ATI development

The rate of ATI development for Remicade (ATI_R) during maintenance use was taken from a meta-analysis [25] as ACCENT I had 46% inconclusive samples and was considered potentially biased [23]. In the base case, this is also the ATI development rate for Inflectra (ATI_I).

2.2.2.Efficacy

Early IFX clinical trials focused on single infusions, and the pivotal maintenance trial, ACCENT I, included only those who had responded to an initial infusion. To provide an estimate of the induction phase response, the probability of response at 12 weeks was taken from an observational study [26].

The rates of loss of response (LOR) by ATI status were derived from a meta-analysis of the impact of antibodies on clinical outcomes [27]. Rates of remission and response by ATI status at 1 year were calculated by adjusting the rates calculated by Saito et al [28] proportionately by the LOR probabilities.

The probabilities of outcomes for standard care were derived from a cohort study by Silverstein et al [17,29]. Patients were divided between the surgery and moderate-to-severe disease outcomes in proportion to the ratio between the probabilities in Kaplan et al [17] (Table 1).

2.2.3.Adverse events

The probabilities of infusion reactions by ATI status were calculated from a meta-analysis of the impact of antibodies on the risk of infusion reactions, with supplementary data from its lead author [30]. Data on mortality from serious adverse events were used for the calculation of associated risk [28].

2.2.4.Utilities

Utility values for disease states and surgery were taken from published cost-effectiveness models [31,32], based upon utility scores defined by Gregor et al [33] using a standard gamble approach. Acute and delayed infusion reactions do not affect disease activity but a 0.01 utility decrement was applied per event [34]. In the absence of other utility estimates, we made the following assumptions: utility for a severe infusion reaction equalled that for surgery; and post-surgical utility equalled moderate-to-severe disease for one period, then surgical remission for the remainder of the year.

2.2.5.Resource use

Patients receiving IFX (and other biologics) also receive standard care. We assumed no vial sharing so each infusion required 4 vials and an NHS day case hospital attendance [35]. Acute infusion reactions were managed at the time of infusion within the day case hospital attendance. Delayed infusion reactions required an additional outpatient clinic visit. Severe infusion reactions were assumed to require a 4 night hospital stay, based on a study of another biologic agent [36], which aligns with a long stay non-elective hospital admission. We assumed that post-surgical therapy was in line with standard care resource use for moderate-to-severe disease.

2.2.6.Costs

Standard care costs were taken from a previous Markov model, inflated using the retail price index [35,37]. The prices of all biologics were from the British National Formulary (BNF) [38–40]. The costs of day-case hospital attendances, outpatient clinic visits and long stay non-elective admissions were from contemporary NHS reference costs [35]. All costs are in pounds Sterling (£).

2.3. Outcomes

Estimates of efficacy, development of ATI and adverse events for Inflectra were assumed equivalent to Remicade in the base case analysis, in line with the assumption of biosimilarity. The outcomes of the analyses were 1-year costs and QALYs for treatment, and the proportion of patients who: experienced sustained remission for 12 months, remission, no adverse events following IFX treatment for 12 months, moved to standard care, developed ATIs, non-response (primary and secondary), infusion reactions (acute, delayed and serious) and surgeries.

Comparative value was determined from the Incremental Net Health Benefit (INHB), which is the difference in Net Health Benefit (NHB) between each intervention [16]. INHB was calculated as the incremental benefit (in QALYs) of the biosimilar compared with the originator, minus the incremental cost divided by the threshold for cost-effectiveness:

Equation 1: Incremental net health benefit (INHB)

$$INHB = (E_I - E_R) - (C_I - C_R)/\lambda$$

Where E and C are the expected benefit (QALY) and costs for Inflectra (I) and Remicade (R), respectively, and λ is the cost-effectiveness threshold for a QALY (assumed £30,000) [41].

2.4. Sensitivity analyses

One-way deterministic analyses were performed for all variables to determine the thresholds over which the risks associated with biosimilar therapy outweigh the benefits, indicated by a negative INHB. Where available, ranges were based on confidence intervals, otherwise we assumed plausible ranges. The results were presented in a tornado plot to examine the impact on INHB.

A two-way sensitivity analysis was conducted to assess the interaction between the development of ATI_I and the price differential between the two drugs. This identifies the discount in vial price required to compensate for a higher rate of antibodies to Inflectra.

A probabilistic sensitivity analysis (PSA) with 10,000 Monte Carlo draws from distributions was conducted. All parameters were included in the PSA except the following fixed costs: Inflectra and Remicade vial costs and NHS costs for short-stays, long-stays and day cases. Efficacy, adverse event and utility parameters were drawn from beta distributions; Dirichlet distributions were used for related parameters (i.e. disease state and outcomes of standard care); and costs for surgery and disease state-related standard and supportive care were drawn from gamma or lognormal distributions (Table 1). We assumed that the unknown biosimilar standard deviations for the rate of initial response and development of ATI were 50% higher than the originator drug to reflect the uncertainty in efficacy and immunogenicity.

2.5. Scenario analyses

To test the robustness of the assumptions in the base case, we considered seven scenarios with alternative assumptions (Table 2). Patients in scenarios (v) to (vii) all have a washout period of six weeks prior to starting a second biologic whereupon they receive standard care. Standard care is continued when starting the new therapy, under the same assumptions of the base case. Patients

who switch following a severe infusion reaction continue their response to IFX until it is lost at week 33. However, an improvement in disease course prompted by the second biologic will override the IFX response. Patients who change biologic following primary or secondary non-response experience moderate-to-severe disease during the washout period and until the new therapy takes effect. LOR for UST and VED was assumed to occur in line with IFX. Adverse events were not modelled for the second-line biologics.

Initial response rates to ADA at week 12 in the IFX failure population were taken from an open label trial as the best match for the dose and timing of outcomes [45], and no LOR was assumed over the year [46]. Initial response to UST at 16 weeks, and sustained remission at 44 weeks, were based on a clinical trial for UST in the IFX failure population [47,48]. The initial response for VED was taken from GEMINI-3, a pivotal study of induction therapy in anti-TNFα failure patients [49]. The week 10 response rate was used as a week 14 rate was unavailable. Sustained remission in anti-TNFα failure patients at week 52 was from a study that used licensed doses of VED [50]. The GEMINI-3 ratio of week 10 response to remission was applied to the long-term remission to calculate long-term response.

UST and VED infusions use single vials and require a day case hospital attendance. ADA and UST subcutaneous injections are patient-administered and are assumed to require no additional resource.

2.6. Value of information analysis

A value of information analysis was conducted using the Sheffield Accelerated Value of Information (SAVI) [51] to identify the value of reducing uncertainty in the model. This was used to assess the value of conducting further clinical research. We calculated the annual expected value of perfect information (EVPI) per patient, and the annual and 10-year population EVPI estimated based on the number of patients affected by Crohn's disease each year in England [52]. A partial EVPI analysis (EVPPI) was conducted to examine the value in reducing the uncertainty in individual model parameters.

2.7. Discounting

We did not apply a discount rate to the model results, as they did not extend beyond a year. A discount rate of 3.5% per annum was applied to the population EVPI.

2.8. Model validation

We performed model validation by: (i) systematically checking the model formulae and inputs; (ii) conducting a number of sensitivity analyses using null and extreme values to ensure results were in the expected direction and within plausible limits; and (iii) comparing the clinical end points from the model with source data.

2.9. Reporting

The analysis is reported in line with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [53].

3. Results

3.1. Base case

The base case analysis results in expected one-year QALYs of 0.803 for both Inflectra and Remicade, with expected one-year costs of £18,087 (USD 25,109) and £19,176 (USD 26,620), respectively (Table 3). The additional benefit of Inflectra to society, based solely on the reduced cost of Inflectra as the health outcomes are equivalent, is represented in the 0.04 (95% Central Range 0.00-0.09) incremental net health benefit (INHB) versus Remicade. Clinical outcomes for both treatments are shown in Table 3.

3.2. Sensitivity analyses

One-way sensitivity analyses demonstrated that the model was most sensitive to the Inflectra vial price and initial response rates of Inflectra and Remicade (Figure 2). The INHB was stable for most model parameters, which were able to take extreme values without altering the result that Inflectra has a positive benefit-risk profile. The INHB advantage of Inflectra was outweighed in the model only when the vial price exceeded that of Remicade.

A two-way sensitivity analysis of the base case (Figure 3) shows how the Inflectra vial price would need to adjust in response to increasing rates of developing ATI in order for it to remain the preferred choice. Based on a cost-effectiveness threshold of £30,000 per QALY [40], and assuming 50% of patients develop ATI for Inflectra (ATI_I), compared with 12.4% who develop ATI from Remicade (ATI_R), then 57.7% of patients would switch to standard care after experiencing a serious infusion reaction or secondary non-response and, within that, 18% of patients would have a surgery. Inflectra remained the preferred option provided it is priced below £410 per vial (compared with £420 for Remicade). Even in a worst-case scenario of all patients developing ATI, resulting in 75% of patients moving to standard care and 23% having surgeries, a vial of Inflectra could be priced up to £395 and it would remain the treatment of choice with a positive INHB (Figure 3, base case).

3.3. Probabilistic sensitivity analyses

The probabilistic sensitivity analyses indicated that Inflectra had a positive INHB in 97.6% of simulations, and this result was robust over a range of threshold values. Inflectra dominated Remicade in 50.4% of simulations and was less effective but less costly in 45.4% of simulations. Inflectra was more effective but more costly in 3.4% and was dominated by Remicade in 0.9% of simulations. The net-benefit plane [53] illustrating the joint distribution of incremental costs and QALYs (Figure 4) shows the clustering of simulations on the vertical axis due to the minimal differences in QALYs between the two interventions.

3.4. Scenario analyses

Inflectra is associated with a positive INHB across the scenarios tested, with the exception of scenario (i) where the price of Remicade is reduced by 25% (Table 3). Changes in INHB overall were minimal and, in fact, there was no change in INHB in scenarios involving a shorter wash-out of IFX following a SIR (iii), a shorter time to loss of response in patients with ATI (iv) and a switch to another biologic before standard care, (v), (vi) and (vii), as changes affected both biologics equivalently.

The results of the two-way sensitivity analysis reveal the value-based price for Inflectra as they identify the price at which the biosimilar could be marketed based upon the development of ATI and downstream consequences [55]. Most scenarios follow a similar pattern to the base case analysis (Figure 3). The price of Inflectra must reduce as ATI_I increases, to remain the optimal choice, but remains below the current market price at all risks of ATI development. Only in scenario (vii), where patients switch to vedolizumab after IFX failure, is a reduction to below the current market price necessary to remain the optimal choice, and it does so when 60% of Inflectra patients develop ATI.

The relationship is reversed in scenario (iv) and the price of Inflectra can increase as ATI_I risk increases, due to the expected cost savings from the earlier movement to standard care. The cost reduction outweighs the QALY reduction, giving Inflectra an even greater net benefit than in the base case. For illustration, when all Inflectra patients develop ATI, the expected QALY gain is 0.03 less than for Remicade whilst resulting in a cost saving of £1,029. A similar pattern is seen for scenario (v) when patients switch to ADA after IFX failure. In this case, the introduction of a second biologic reduces costs as it is cheaper than IFX, but also reduces the number of patients moving to standard care in the model and therefore limits the number of expensive surgeries as ATI_I increases.

3.5. Value of information analysis

Using the results of the probabilistic sensitivity analysis (PSA), the expected value of perfect information (EVPI) in the base case analysis is £7.56 per patient. Based on the number of patients expected to be eligible for Inflectra in England (7,912) [52], the value of removing the decision uncertainty is £59,775 for one year and £807,332 for the assumed 20-year therapeutic lifetime of the drug. This represents the upper limit on the investment of conducting further research to eliminate uncertainty in model parameters. A more informative expected value of partial perfect information (EVPPI) indicates that there would be no gain from any research to reduce uncertainty in any individual parameters, including the ATI rate of Inflectra.

The result of the second VOI analysis, where the price of Remicade is reduced to match that of Inflectra, provides a different result. In this case, the EVPI increases to £220.51 per person, equivalent to £25.4 million (discounted) for the 20-year assumed therapeutic lifespan. The EVPPI is now relevant and the highest value is for the initial response rate of Inflectra, where the expected value of reducing uncertainty is £196.42 per patient, which is £1.6 million per year, or £22.6 million over 20 years. There is greater value in reducing uncertainty from a range of parameters, including the initial response rate of Remicade, and the rates of sustained remission, sustained response and loss of response in patients who do not develop ATI, than in reducing uncertainty in ATI_I, which has an EVPPI of £7.00 per patient.

3.5. Model validation

Systematic checks did not reveal any errors in formulae and inputs. The sensitivity analyses demonstrated the model behaved as expected. The clinical endpoints from the model aligned with source data.

4. Discussion

This is the first study to explicitly consider the trade-off between the risk of development of ATI (which is largely unknown at the time of marketing authorisation) and cost advantages of biosimilars, and the value of obtaining further evidence. It positions the problem of assessing the benefit-risk of biosimilars in the context of an economic evaluation framework. For Inflectra, the results support the extrapolation process of regulators which deemed the new drug biosimilar to the originator [9,10]. Non-inferiority of the biosimilar to the originator infliximab was demonstrated in a phase III trial for rheumatoid arthritis [8] and extrapolation assumes equivalence in efficacy for Crohn's disease. Results from a post-marketing trial of Inflectra and Remicade indicate there is no significant difference between the efficacy and safety of the two drugs at 6 weeks [56]. Observational studies and clinical case series have confirmed that Inflectra appears to be safe and efficacious, especially in infliximab-naïve patients [57]. A study of cross immunogenicity identified that ATI developed in patients treated with Remicade react to the biosimilar, further supporting the case that the two drugs are biosimilar

[58]. More recently, a phase 3, non-inferiority randomised controlled trial demonstrated no notable differences in the efficacy, pharmacokinetics, pharmacodynamics, safety, or immunogenicity of Inflectra and Remicade in the recruited population [59].

A major strength of our study is the transparency the approach provides for assessing the value of biosimilars, taking into account both benefits (in terms of cost savings) and the uncertainty of potential harms. Biosimilars are promoted as suitable alternatives to originator products to restrain healthcare costs; however, the HTA of biosimilars presents significant challenges due to the assumption of equivalence in outcomes and the lack of availability of comprehensive data at the time of marketing authorisation. Our approach overcomes some of these difficulties by making explicit reference to, and characterising the uncertainty of ATI development as the driver for differences in treatment outcomes. This addresses potential areas of concern relating to the extrapolation exercise while allowing for the uncertainty to be quantified – both in terms of identifying whether the cost savings are sufficient for a health-care payer to accept a potentially inferior product, and the value of conducting further research [60]. This is especially relevant in the UK system where biosimilars are not subjected to health technology appraisal, but instead existing guidance for originator drugs is applied to the biosimilar once they have gained marketing approval [61].

By their nature, models that draw from multiple sources of evidence require many assumptions. We were unable to locate evidence linking the risk of cancer or serious infection to ATI development so they were not considered, despite their importance in infliximab use and the likelihood of large cost and utility impacts. Estimates for ATIs were based on the episodic use of infliximab or were complicated by the absence of a standard definition of ATI, the many factors that can affect ATI test result [12] and the increasing recognition of transient ATI, which are idiosyncratic and have little impact on outcomes [62]. No recognition of the relation between ATI concentration and response was made; and factors other than ATI, which are recognised as predictors of response to infliximab in Crohn's disease [63], including drug clearance, were not considered. However, immunogenicity

appears to be the main factor associated with low drug concentrations long term, and may therefore be captured sufficiently in our sensitivity analyses. Further limitations stemmed from the data available on "standard care" for Crohn's disease, which do not accurately reflect current clinical management of CD and which we attempted to overcome by including scenarios with other biologics (adalimumab, vedolizumab and ustekinumab). However, other scenarios might include dose escalation or shortening the interval between infusions prior to switching to another drug or a switch to the originator drug [20]. Further, modelling of second line biologics should consider their harms so as not to overstate their benefits. Addressing some of these points might explain some of the counterintuitive results in the scenarios where increasing risk of immunogenicity with Inflectra can be accompanied with a justified increase in price because switching to alternative therapies is seen as more cost-effective. However, accepting these limitations may be appropriate for a model focused not on predicting outcomes, but rather to offer a transparent and structured way to examine a complex decision problem.

5. Conclusion

In summary, in the absence of trial evidence, the model provides a basis for the quantitative evaluation of biosimilars to support health technology assessment. Value-based pricing using this methodology would be possible to protect health systems such as the NHS in the UK from the potential risks of biosimilars where they are untested in the populations for which they have been approved.

6. Data availability statement

The datasets generated during the current study and the model underpinning the study are available from the corresponding author on reasonable request.

7. Acknowledgements

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review, or approval of the manuscript. D.H. acknowledges the support of Health and Care Research Wales as a Senior Research Leader (SRL/15/029).

8. Compliance with Ethical Standards

Conflicts of interest

H.C., J.K. and D.H. declare that they have no conflicts of interest. K.B. declares a travel grant from Janssen-Cilag Ltd.

Contributions

H.C., D.H., K.B, and J.K. contributed substantially to the study conception or design, or the acquisition, analysis or interpretation of the data. H.C. drafted the manuscript and D.A.H. revised it critically for important intellectual content. H.C., D.H., K.B, and J.K. gave final approval of the version to be published. D.A.H. agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

9. References

1. Committee for Medicinal Products for Human Use (CHMP). Guideline on similar biological medicinal products CHMP/437/04 Rev 1. (2015).
2. Food and Drug Administration. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. Guidance for Industry. (2015).
3. Committee for Medicinal Products for Human Use (CHMP). Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies - non-clinical and clinical issues. EMA/CHMP/BMWP/403543/2010. (2012). doi:10.1089/blr.2011.9970
4. De Mora F. Biosimilar: What it is not. Br J Clin Pharmacol 2015; 80;949–956.
5. Prasad V. Non-Inferiority Trials in Medicine: Practice Changing or a Self-Fulfilling Prophecy? J Gen Intern Med 2018;33:3–5.
6. Stewart A, Aubrey P, Belsey J. Addressing the health technology assessment of biosimilar pharmaceuticals. Curr Med Res Opin 2010;26:2119–2126.
7. Mulcahy AW, Hlavka JP, Case SR. Biosimilar Cost Savings in the United States: Initial Experience and Future Potential [online]. RAND corporation: Perspective (2017). doi:10.7249/PE264
8. Yoo DH, Hrycaj P, Miranda P, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: The PLANETRA study. Ann Rheum Dis 2013;72:1613–1620.
9. Food and Drug Administration. Addendum to Primary Clinical Review. Recommendation on Regulatory Action. Inflectra. (2016).
10. Committee for Medicinal Products for Human Use (CHMP). Assessment report. Inflectra. 44, (2013).
11. Committee for Medicinal Products for Human Use (CHMP). GUIDELINE ON THE DEVELOPMENT OF NEW MEDICINAL PRODUCTS FOR THE TREATMENT OF CROHN'S DISEASE Rev. 2. (2016).
12. Ben-Horin S, Heap GA, Ahmad T, et al. The immunogenicity of biosimilar infliximab: can we extrapolate the data across indications? Expert Rev. Gastroenterol Hepatol 2015;9:27–34.
13. Ben-Horin S, Vande Casteele N, Schreiber S, Lakatos PL. Biosimilars in Inflammatory Bowel Disease : Facts and Fears of Extrapolation. Clin Gastroenterol Hepatol 2016;14:1685–1696.
14. Feagan BG, Choquette D, Ghosh S, et al. The challenge of indication extrapolation for infliximab biosimilars. Biologicals 2014;42:177–183.
15. Weinstein MC, O'Brien B, Hornberger J, et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies. Value Heal. 2003;6:9–17.
16. Stinnett AA, Mullahy J. Net Health Benefits : A New Framework for the Analysis of Uncertainty in Cost-Effectiveness Analysis. Med Decis Mak. 1998;18:S68-80.
17. Kaplan GG, Hur C, Korzenik J, Sands BE. Infliximab dose escalation vs. initiation of adalimumab for loss of response in Crohn's disease: A cost-effectiveness analysis. Aliment Pharmacol Ther. 2007;26:1509–1520.

18. Roda G, Jharap B, Neeraj N, Colombel J-F. Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. Clin Transl Gastroenterol. 2016;7:e135.

19. Cheifetz A, Smedley M, Martin S, et al. The incidence and management of infusion reactions to infliximab: A large center experience. Am J Gastroenterol. 2003;98:1315–1324.

20. Gomollón F, Dignass A, Annese V, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 1: Diagnosis and medical management. J Crohn's Colitis 2017;11:3–25.

21. Medicines.org.uk. Remicade 100mg powder for concentrate for solution for infusion - SUMMARY OF PRODUCT CHARACTERISTICS (SPC). eMC 1–16 (2009). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000240/WC500050888.pdf. (Accessed: 25th June 2018)

22. Terdiman JP, Gruss CB, Heidelbaugh JJ, Sultan S, Falck-Ytter YT. American gastroenterological association institute guideline on the use of thiopurines, methotrexate, and anti-TNF-α biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. Gastroenterology 2013;145:1459–1463.

23. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: The ACCENT I randomised trial. Lancet 2002;359:1541–1549.

24. Office for National Statistics. UK Life Tables 2012-2014. (2016).

25. Lee LYW, Sanderson JD, Irving PM. Anti-infliximab antibodies in inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2012;24:1078–1085.

26. Miheller P, Lakatos PL, Horváth G, et al. Efficacy and safety of infliximab induction therapy in Crohn's Disease in Central Europe - a Hungarian nationwide observational study. BMC Gastroenterol. 2009;9:66.

27. Nanda KS, Cheifetz AS, Moss AC. Impact of antibodies to infliximab on clinical outcomes and serum infliximab levels in patients with inflammatory bowel disease (IBD): a meta-analysis. Am J Gastroenterol 2013;108:40–47.

28. Saito S, Shimizu U, Nan Z, et al. Economic impact of combination therapy with infliximab plus azathioprine for drug-refractory Crohn's disease: A cost-effectiveness analysis. J. Crohn's Colitis 2013;7:167–174.

29. Silverstein MD, Loftus EV, Sandborn WJ, et al. Clinical course and costs of care for Crohn's disease: Markov model analysis of a population-based cohort. Gastroenterology 1999;117:49–57.

30. O'Meara S, Nanda KS, Moss AC. Antibodies to infliximab and risk of infusion reactions in patients with inflammatory bowel disease: a systematic review and meta-analysis. Inflamm Bowel Dis 2014;20:1–6.

31. Siegel CA, Finlayson SRG, Sands BE, Tosteson ANA. Adverse events do not outweigh benefits of combination therapy for crohn's disease in a decision analytic model. Clin Gastroenterol Hepatol. 2012;10:46–51.

32. Ananthakrishnan AN, Hur C, Juillerat P, Korzenik JR. Strategies for the prevention of postoperative recurrence in Crohn's disease: results of a decision analysis. Am J Gastroenterol 2011;106:2009–17.

33. Gregor JC, McDonald JWD, Klar N, Wall R, Atkinson K, Lamba B, Feagan BG. An evaluation of utility measurement in Crohn's disease. Inflamm Bowel Dis 1997; 3:265-276.

34. Doherty GA, Miksad RA, Cheifetz AS, Moss AC. Comparative cost-effectiveness of strategies to prevent postoperative clinical recurrence of Crohn's disease. Inflamm Bowel Dis 2012;18:1608–1616.

35. Curtis L. PSSR Unit Costs of Health and Social Care 2013. (2013).

36. Kasi PM, Tawbi HA, Oddis CV, Kulkarni HS. Clinical review: Serious adverse events associated with the use of rituximab - a critical care perspective. Crit Care 2012;16:231.

37. Bodger K, Kikuchi T, Hughes, D. Cost-effectiveness of biological therapy for Crohn's disease: Markov cohort analyses incorporating United Kingdom patient-level cost data. Aliment Pharmacol Ther. 2009;30:265–274.

38. National Institute for Health and Care Excellence. Infliximab and adalimumab for the treatment of Crohn's disease - TA187. 1–44 (2010).

39. National Institute for Health and Care Excellence. Ustekinumab for treating moderately to severely active Crohn's disease after previous treatment - Technology appraisal guidance TA456. (2017).

40. National Institute for Health and Care Excellence. Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy - Technology appraisal guidance TA352. (2015). Available at: nice.org.uk/guidance/ta352. (Accessed: 1st July 2018)

41. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. (2013). doi:10.2165/00019053-200826090-00002

42. medicines.org.uk. Humira 40mg solution for injection in pre-filled syringe - SUMMARY OF PRODUCT CHARACTERISTICS (SPC). eMC (2003). Available at: https://www.medicines.org.uk/emc/product/2150/smpc#CLINICAL_PARTS. (Accessed: 10th July 2018)

43. medicines.org.uk. STELLARA 90mg solution for injections - Summary of Product Characteristics (SPC). eMC (2009). Available at: https://www.medicines.org.uk/emc/product/4413/smpc. (Accessed: 10th July 2018)

44. medicines.org.uk. Entyvio 300mg powder for concentrate for solution for infusion - Summary of Product Characteristics (SPC). eMC (2014). Available at: https://www.medicines.org.uk/emc/product/5442/smpc. (Accessed: 10th July 2018)

45. Sandborn WJ, Hanauer S, Loftus EV Jr, et al. An open-label study of the human anti-TNF monoclonal antibody adalimumab in subjects with prior loss of response or intolerance to infliximab for Crohn's disease. Am J Gastroenterol. 2004;99:1984–1989.

46. Da W, Zhu J, Wang L, Lu Y. Adalimumab for Crohn's disease after infliximab treatment failure. Eur J Gastroenterol Hepatol. 2013;25:885–891.

47. Colombel J-F, Sloan S, Gasink C, et al. A147 Response and remission after 16 weeks of ustekinumab - an all patients analysis from the UNITI Crohn's studies. J Can Assoc Gastroenterol. 2018;1(suppl 2):219–220.

48. Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 2016;375:1946-1960.

49. Sands BE, Feagan BG, Rutgeerts P, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. Gastroenterology 2014;147:618–627.e3.

50. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 2013;369:711–721.

51. Strong M, Oakley JE, Brennan A. Estimating Multiparameter Partial Expected Value of Perfect Information from a Probabilistic Sensitivity Analysis Sample. Med Decis Mak. 2014;34:311–326.

52. National Institute for Health and Care Excellence. Infliximab and Adalimumab for the Treatment of Crohn's Disease Costing Template and Report - Technology Appraisal Guidance 187. (2010).

53. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--Explanation and elaboration: A report of the ISPOR Health Economic Evaluations Publication Guidelines Task Force. Value Heal. 2013;16:231–250.

54. Lynd LD, O'Brien BJ. Advances in risk-benefit evaluation using probabilistic simulation methods: An application to the prophylaxis of deep vein thrombosis. J Clin Epidemiol. 2004;57:795–803.

55. Breeze P, Brennan A. Valuing trial designs from a pharmaceutical perspective using value-based pricing. Heal Econ. 2014;18:S37–S54.

56. Kim YH, Ye BD, Pesegova M, et al. DOP061 Phase III randomised, double-blind, controlled trial to compare biosimilar infliximab (CT-P13) with innovator infliximab in patients with active Crohn's disease: early efficacy and safety results. J Crohn's Colitis 2017;11:S62.

57. Fiorino G, Manetti N, Armuzzi A, et al. The PROSIT-BIO Cohort: A Prospective Observational Study of Patients with Inflammatory Bowel Disease Treated with Infliximab Biosimilar. Inflamm Bowel Dis 2017;23:233–243.

58. Ben-Horin S, Yavzori M, Benhar I, et al. Cross-immunogenicity: antibodies to infliximab in Remicade-treated patients with IBD similarly recognise the biosimilar Remsima. Gut 2016;65:1132–8.

59. Ye BD, Pesegova M, Alexeeva O, et al. Efficacy and safety of biosimilar CT-P13 compared with originator infliximab in patients with active Crohn's disease: an international, randomised, double-blind, phase 3 non-inferiority study. Lancet. 2019;393(10182):1699-1707

60. Acha V, Mestre-Ferrandiz J. Translating European regulatory approval into healthcare uptake for biosimilars: the second translational gap. Technol Anal Strateg Manag. 2017;29:263–275.

61. National Institute for Health and Care Excellence. NICE's Biosimilar Position Statement. 7–8 (2014).

62. Ungar B, Chowers Y, Yavzori M, et al. The temporal evolution of antidrug antibodies in patients with inflammatory bowel disease treated with infliximab. Gut 2014;63:1258–64.

63. Kennedy NA, Heap GA, Green HD, et al; UK Inflammatory Bowel Disease Pharmacogenetics Study Group. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. Lancet Gastroenterol Hepatol. 2019 May;4(5):341-353.

Figure legends

Figure 1: Partial schematic representation of the decision-analysis model comparing Inflectra and Remicade. Standard care arm shown in offset box. Abbreviations: ATI – Antibodies to infliximab, LOR – loss of response

Figure 2: Tornado plot of univariate analysis. Panel presents the ten parameters that led to the greatest change in overall incremental net health benefits (INMB). Inflectra parameters (suffixed _I), Remicade parameters (suffixed _R). L/H refer to lower and higher limits of parameter estimates. Abbreviations: ATI – Antibodies to infliximab, LOR – loss of response, IR – infusion reaction

Figure 3: Results of the two-way analysis of risk of Inflectra antibodies (ATI) against incremental vial price. Each figure represents a scenario. Scenario (i), 25% reduction in vial cost of Remicade; Scenario (ii), patients with secondary non-response but no adverse events continue treatment; Scenario (iii), 8 week infliximab wash out period; Scenario (iv), secondary non-response at 15 weeks for those developing ATI; Scenario (v), switch to adalimumab after IFX failure; Scenario (vi), switch to ustekinumab after IFX failure; and Scenario (vii), switch to vedolizumab after IFX failure.

Figure 4: Net-benefit plane resulting from probabilistic sensitivity analysis. The line represents the cost-effectiveness threshold of £30,000 per quality-adjusted life year (QALY).

Table 1: Clinical event rates, health state utilities assigned to clinical events, and costs

Parameter estimate	Base	Range for univariate sensitivity analysis low	high	Distribution for probabilistic sensitivity analysis	Ref.
Antibodies to infliximab (ATI) probability					
ATI development during maintenance use[a]	0.124	0.108	0.141	Beta_R(95,19) Beta_I(6,1)	[25]
Efficacy transition probabilities					
Initial response to infliximab at 12 weeks[b]	0.833	0.667	1	Beta_R(195,1383) Beta_I(84,594)	[26]
ATI+ responders in remission at 12 months	0.21	N/A	N/A	Dir(30)	[27,28]
ATI+ responders in response at 12 months	0.121	N/A	N/A	Dir(18)	[27,28]
ATI+ responders lost response at 12 months[b]	0.669	0.535	0.803	Dir(97)	[27]
ATI- responders in remission at 12 months	0.482	N/A	N/A	Dir(187)	[27,28]
ATI- responders in response at 12 months	0.278	N/A	N/A	Dir(108)	[27,28]
ATI- responders lost response at 12 months[b]	0.24	0.192	0.288	Dir(93)	[27]
Adverse event transition probabilities					
ATI+ responders experience acute IR[b]	0.315	0.252	0.378	Beta(78.170)	[30]
ATI+ responders experience delayed IR[b]	0.054	0.043	0.065	Beta(7,122)	[30]
ATI+ responders experience severe IR[b]	0.094	0.075	0.113	Beta(10,96)	[30]
ATI- responders experience acute IR[b]	0.142	0.114	0.17	Beta(133,804)	[30]
ATI- responders experience delayed IR[b]	0.021	0.017	0.025	Beta(12,569)	[30]
ATI- responders experience severe IR[b]	0.061	0.049	0.073	Beta(3,46)	[30]
Death from severe IR[c]	0.004	0	0.01	Beta(2,609)	[28]
Age-specific all-cause mortality[c]	0.001	0	0.005	Beta(1,630)	[24]
Adalimumab therapy					
12 week remission rate	0.29			N/A	[44]
12 week response rate	0.39			N/A	[44]
12 week no response rate	0.41			N/A	[44]
Ustekinumab therapy					
Initial response at week 16	0.474				[46]
Responders in remission at week 44	0.386				[47]
Responders in response at week 44	0.312				[47]
Responders lost response at week 44	0.302				[47]
Vedolizumab therapy					
Initial response at week 10					[48]
Responders in remission at week 52	0.280				[48,49]
Responders in response at week 52	0.213				[48,49]
Responders lost response at week 52	0.507				[48,49]
Standard care therapy [d]					
Remain moderate-to-severe disease	0.680	0.544	0.816	Dir(30)	[17,29]
Require surgery[b]	0.312	0.250	0.375	Dir(14)	[17,29]
Death from surgery	0.002	N/A	N/A	Beta(96,63831)	[17,29]
Death from Crohn's disease flare	0.008	N/A	N/A	Dir(0.3)	[17,29]
Quality of life utilities					
Medical remission[e]	0.89	0.67	1	Beta(11,1)	[31,32]

Parameter estimate	Base	Range for univariate sensitivity analysis low	high	Distribution for probabilistic sensitivity analysis	Ref.
Mild disease[e]	0.81	0.61	1	Beta(12,3)	[31,32]
Moderate-to-severe disease[e]	0.74	0.56	0.93	Beta(15,5)	[31,32]
Surgery[e]	0.4	0.3	0.5	Beta(36,55)	[31,32]
Surgical remission[e]	0.8	0.6	1	Beta(11,3)	[31,32]
Severe infusion reaction[e]	0.4	0.3	0.5	Beta(36,55)	[31,32]
Utility decrement per acute or delayed IR[c]	0.01	0	0.1	Beta(0.1,14)	[33]
Death	0	N/A	N/A		
Costs (GBP)					
Inflectra vial cost[f]	378	189	420	N/A	
Remicade vial cost	420	N/A	N/A	N/A	[37]
Adalimumab subcutaneous injection cost	358	N/A	N/A	N/A	[37]
Ustekinumab vial & subcutaneous injection cost	2,147	N/A	N/A	N/A	[38]
Vedolizumab vial cost	2,050	N/A	N/A	N/A	[39]
Infusion (day case hospital attendance)	697	N/A	N/A	N/A	[34]
Remission therapy (4 weeks) [e]	58	43	72	Lognormal(4.1,0.1)	[34,36]
Mild disease therapy (4 weeks) [e]	165	123	206	Gamma(61.5,2.7)	[34,36]
Moderate-to-severe disease therapy (4 weeks) [e]	257	193	321	Gamma(61.5,4.2)	[34,36]
Post-surgery therapy (4 weeks)[g]	257	129	386	Gamma(15.4,16.7)	[34,36]
Surgery[e]	11,116	8,337	13,894	Gamma(61.5,180.9)	[34,36]
Delayed IR (outpatient hospital attendance)	135	N/A	N/A	N/A	[34]
Severe IR (non-elective long stay admission)	2,581	N/A	N/A	N/A	[34,35]

Note:
Parameter values are identical in the base case for both treatments due to the assumption of biosimilarity.
IR: infusion reaction.
ATI+ patients who developed antibodies to infliximab
ATI- patients who did not develop antibodies to infliximab
_R indicates distribution for Remicade parameter and _I for Inflectra parameter

a reported confidence interval used as range
b reported mean +/-20% used as range
c range determined by authors
d Silverstein standard care outcomes with remission and response parameters shared proportionately between moderate to severe disease and surgery outcomes to reflect more severe disease pathway.
e reported mean +/- 25% used as range
f BNF reported prices, range of 50% to 100% of Remicade price
g reported mean +/- 50% used as range, to account for uncertainty in costs

Table 2: Scenario analyses.

Scenario	Assumption tested
(i)	25% reduction in the price of Remicade® in response to the biosimilar entrance to the market.
(ii)	Patients who had not experienced any adverse event continuing with IFX despite secondary non-response, and remaining in the moderate-to-severe disease state.
(iii)	Shorter washout period of 8 weeks in those who experienced a severe infusion reaction and stopped IFX therapy.
(iv)	Shorter time to loss of response (LOR) in patients who developed ATIs (lower quartile of the interquartile range from ACCENT I) [23] to reflect the potential for increased clearance of the drug due to antibodies.
(v)	Patients switch to adalimumab (ADA) upon IFX failure. Therapy begins with an 80mg subcutaneous injection in week 0, followed by 40mg in week 2 and every other week as per the product label [41]. Initial response is checked at week 12 and patients transition to standard care if no response.
(vi)	Patients switch to ustekinumab (UST) upon IFX failure. UST is infused at an initial dose of 6mg/kg, with further therapy (90mg) administered subcutaneously at week 8 and every subsequent 12 weeks [42]. Initial response is checked at week 16 and patients transition to standard care if no response [42].
(vii)	Patients switch to vedolizumab (VED) upon IFX failure. VED is administered as 300mg infusions at weeks 0, 2 and 6, followed by maintenance infusions at week 14 and every 8 weeks after [43]. Initial response is checked at week 14 and patients move to standard care if no response.

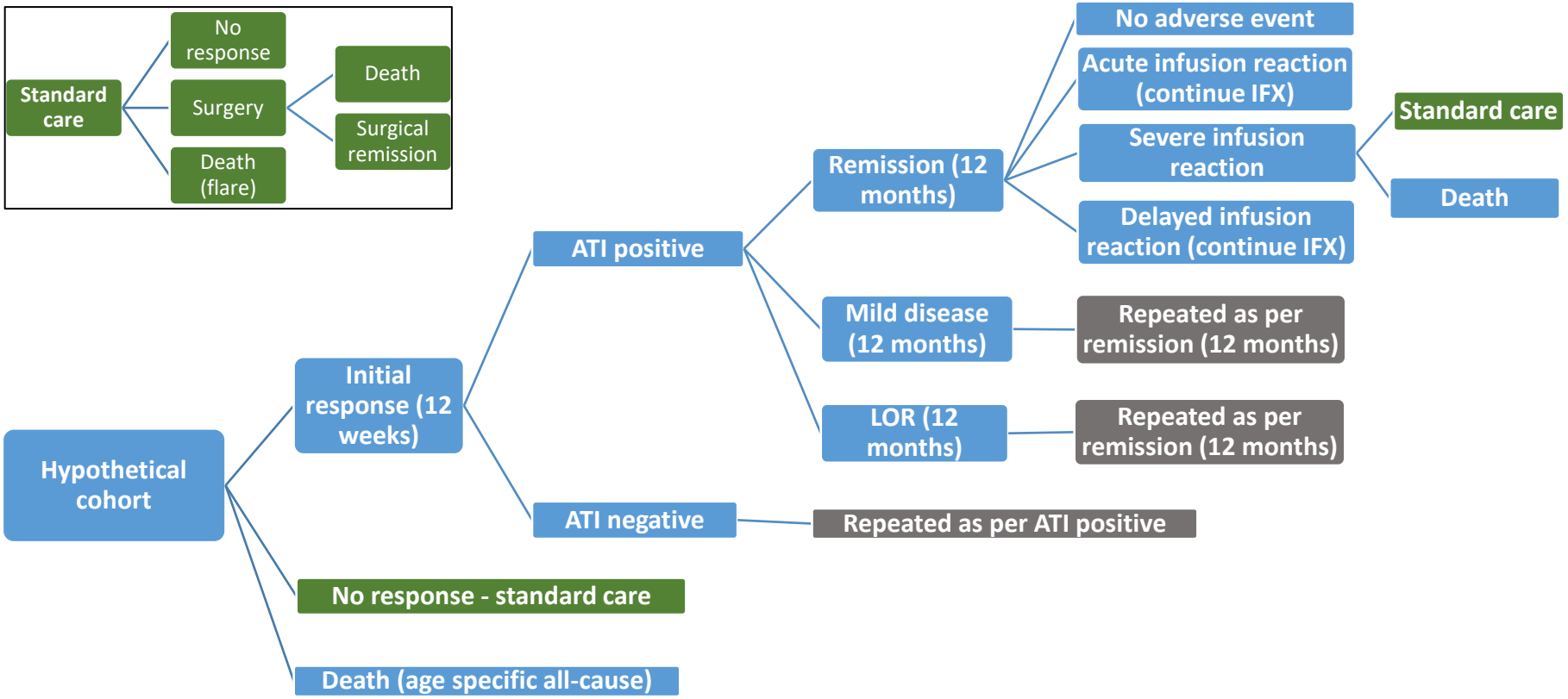
Table 3: Model results for base case and scenarios.

		Base case	(i) Remicade price drop	(ii) LOR no AEs continue IFX	(iii) 8 week wash-out after SIR ends IFX	(iv) Shorter time to LOR with ATI	(v) Switch to ADA upon IFX failure	(vi) Switch to UST upon IFX failure	(vii) Switch to VED upon IFX failure
Vial cost	Inflectra	£ 378	£ 378	£ 378	£ 378	£ 378	£ 378	£ 378	£ 378
	Remicade	£ 420	£ 315	£ 420	£ 420	£ 420	£ 420	£ 420	£ 420
Expected QALY	Inflectra	0.803	0.803	0.803	0.802	0.801	0.816	0.811	0.813
	Remicade	0.803	0.803	0.803	0.802	0.801	0.816	0.811	0.813
Expected cost	Inflectra	£ 18,087	£ 18,087	£ 18,729	£ 18,097	£ 17,821	£ 18,166	£ 19,421	£ 21,366
	Remicade	£ 19,176	£ 16,453	£ 19,867	£ 19,187	£ 18,890	£ 19,255	£ 20,511	£ 22,455
Net health benefit	Inflectra	0.200	0.200	0.179	0.199	0.207	0.211	0.164	0.101
	Remicade	0.164	0.254	0.141	0.162	0.172	0.174	0.128	0.064
Incremental	QALY	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Cost	-£ 1,089	£ 1,634	-£ 1,138	-£ 1,089	-£ 1,069	-£ 1,089	-£ 1,089	-£ 1,089
	NHB	0.036	-0.054	0.038	0.036	0.036	0.036	0.036	0.036
	Vial cost	-£ 42	£ 63	-£ 42	-£ 42	-£ 42	-£ 42	-£ 42	-£ 42
	ICER	Dominant	Dominated	Dominant	Dominant	Dominant	Dominant	Dominant	Dominant
Clinical outcomes	Sustained remission	35.0%	35.0%	35.0%	35.0%	35.0%	35.7%	35.4%	35.7%
	Remission	48.9%	48.9%	48.9%	48.9%	48.9%	50.1%	43.2%	51.3%
	IFX for 12 months with no AEs	44.8%	44.8%	62.2%	44.8%	44.8%	44.8%	44.8%	44.8%
	Standard care	44.8%	44.8%	27.5%	44.8%	44.8%	18.4%	29.9%	27.7%
	Developed ATIs	10.3%	10.3%	10.3%	10.3%	10.3%	10.3%	10.3%	10.3%
	Primary non-response	16.6%	16.6%	16.6%	16.6%	16.6%	16.6%	16.6%	16.6%
	Secondary non-response	24.4%	24.4%	24.4%	24.4%	24.4%	24.4%	24.4%	24.4%
	Deaths	0.5%	0.5%	0.5%	0.5%	0.5%	0.2%	0.2%	0.2%
	Acute infusion reactions	13.6%	13.6%	13.6%	13.6%	13.6%	13.6%	13.6%	13.6%
	Severe infusion reactions	5.4%	5.4%	5.4%	5.4%	5.4%	5.4%	5.4%	5.4%
	Delayed infusion reactions	2.1%	2.1%	2.1%	2.1%	2.1%	2.1%	2.1%	2.1%

Surgeries	14.0%	14.0%	14.0%	14.0%	14.0%	2.8%	3.6%	3.6%

Note: Scenario (i), 25% reduction in vial cost of Remicade; Scenario (ii), patients with secondary non-response but no AEs continue treatment; Scenario (iii), 8 week IFX wash out period; Scenario (iv), secondary non-response at 15 weeks for those developing ATIs; Scenario (v), patients switch to adalimumab before standard care; Scenario (vi), patients switch to ustekinumab before standard care; Scenario (vii), patients switch to vedolizumab before standard care.

Abbreviations: QALY - quality adjusted life year; NHB - net health benefit; ICER - incremental cost effectiveness ratio; IFX – infliximab; AEs - adverse events; ATI - antibodies to infliximab; SIR – severe infusion reaction; LOR – loss of response; ADA – adalimumab; UST – ustekinumab; VED - vedolizumab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Surgery
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Death
Surgical remission
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ATI negative
Remission (12 months)
Mild disease (12 months)
LOR (12 months)
No adverse event
Acute infusion reaction (continue IFX)
Severe infusion reaction
Delayed infusion reaction (continue IFX)
Standard care
Death
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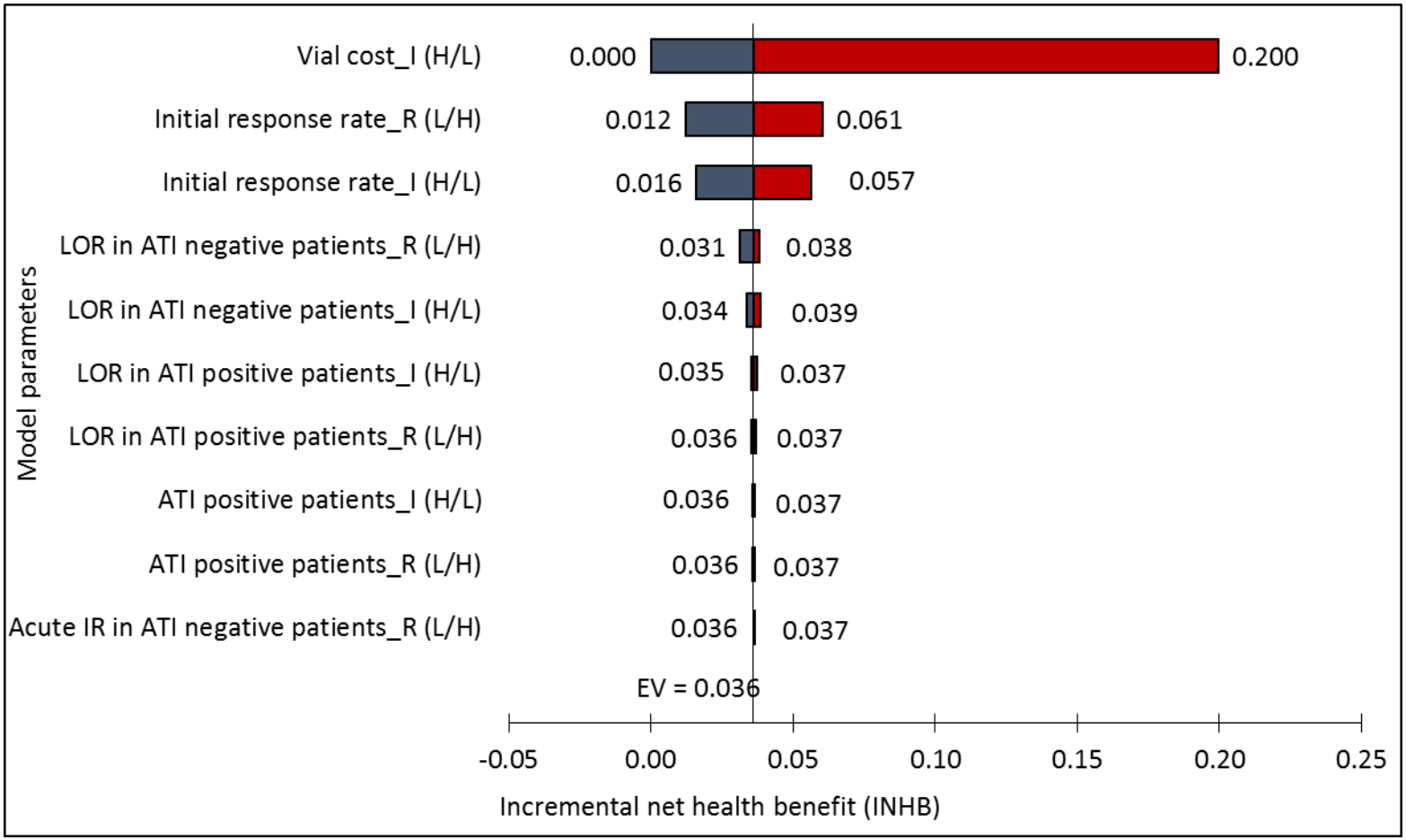
Repeated as per remission (12 months)
Repeated as per ATI positive
No response - standard care
Death (age specific all-cause)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0.061
Initial response rate_I (H/L)
0.016
0.057
LOR in ATI negative patients_R (L/H)
0.031
0.038
LOR in ATI negative patients_I (H/L)
0.034
0.039
LOR in ATI positive patients_I (H/L)
0.035
0.037
LOR in ATI positive patients_R (L/H)
0.036
0.037
ATI positive patients_I (H/L)
0.036
0.037
ATI positive patients_R (L/H)
0.036
0.037
Acute IR in ATI negative patients_R (L/H)
0.036
0.037
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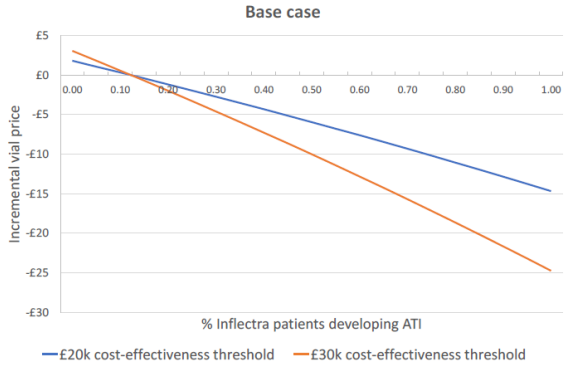
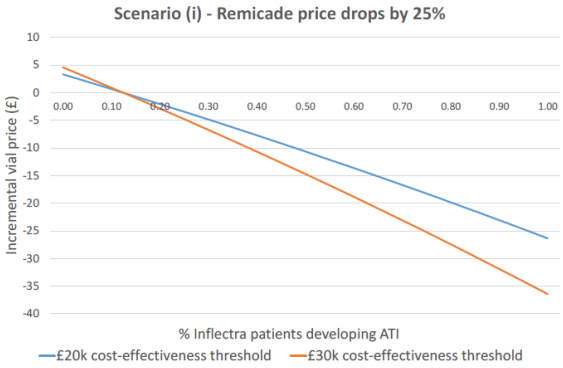
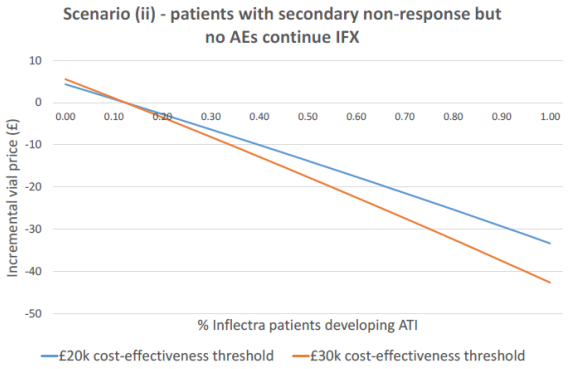
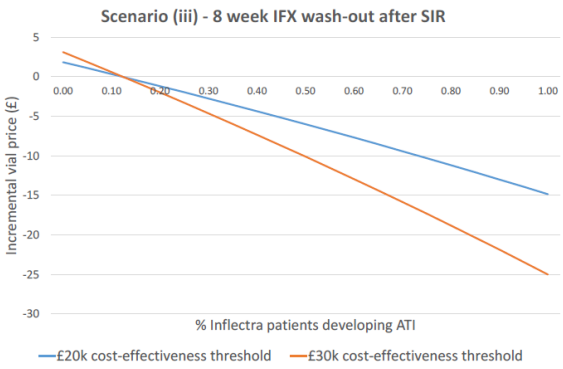
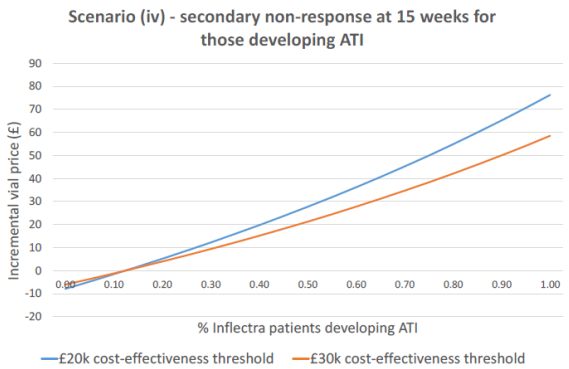
0.00
0.05
0.10
0.15
0.20
0.25
Incremental net health benefit (INHB)

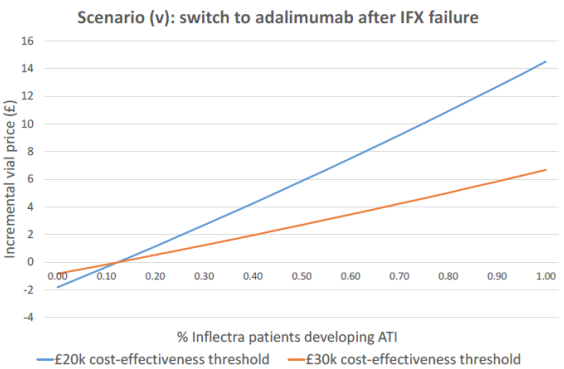

Base case
Incremental vial price
% Inflectra patients developing ATI
£20k cost-effectiveness threshold
£30k cost-effectiveness threshold

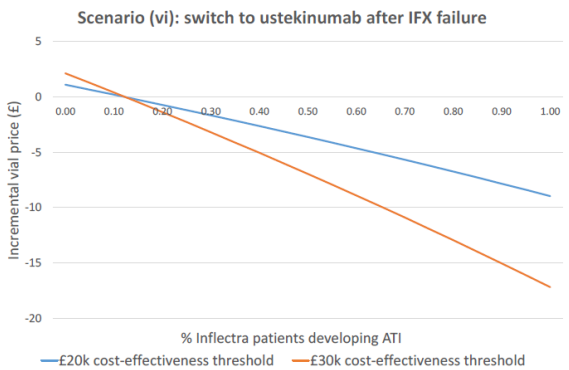

Scenario (i) - Remicade price drops by 25%
Incremental vial price (£)
% Inflectra patients developing ATI
£20k cost-effectiveness threshold
£30k cost-effectiveness threshold

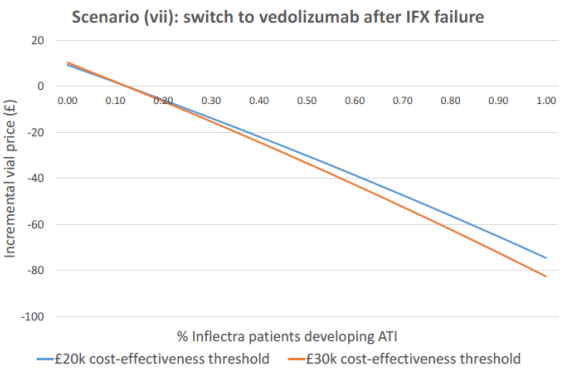

Scenario (ii) - patients with secondary non-response but no AEs continue IFX
Incremental vial price (£)
% Inflectra patients developing ATI
£20k cost-effectiveness threshold
£30k cost-effectiveness threshold

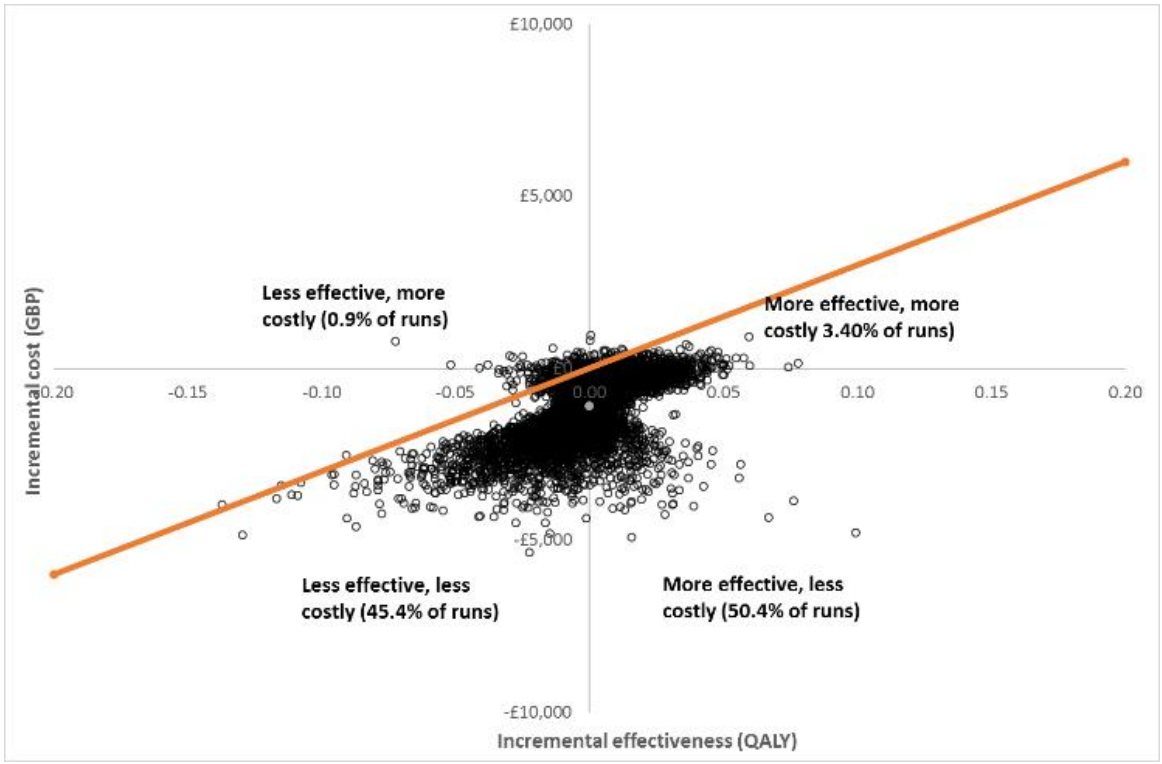

Scenario (iii) - 8 week IFX wash-out after SIR
Incremental vial price (£)
% Inflectra patients developing ATI
£20k cost-effectiveness threshold
£30k cost-effectiveness threshold


Scenario (iv) - secondary non-response at 15 weeks for those developing ATI
Incremental vial price (£)
% Inflectra patients developing ATI
£20k cost-effectiveness threshold
£30k cost-effectiveness threshold


Scenario (v): switch to adalimumab after IFX failure
Incremental vial price (£)
% Inflectra patients developing ATI
£20k cost-effectiveness threshold
£30k cost-effectiveness threshold


Scenario (vi): switch to ustekinumab after IFX failure
Incremental vial price (£)
% Inflectra patients developing ATI
£20k cost-effectiveness threshold
£30k cost-effectiveness threshold


Scenario (vii): switch to vedolizumab after IFX failure
Incremental vial price (£)
% Inflectra patients developing ATI
£20k cost-effectiveness threshold
£30k cost-effectiveness threshold


£10,000
£5,000
Less effective, more costly (0.9% of runs)
More effective, more costly 3.40% of runs)
Incremental cost (GBP)
-0.20
-0.15
-0.10
-0.05
0.00
0.05
0.10
0.15
0.20
-£5,000
Less effective, less costly (45.4% of runs)
More effective, less costly (50.4% of runs)
-£10,000
Incremental effectiveness (QALY)